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Early microcirculatory impairment during therapeutic hypothermia is associated with poor outcome in post-cardiac arrest children: A prospective observational cohort study

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ABSTRACT

Aims of the study: This study aimed to evaluate if the microcirculation is impaired during and after therapeutic hypothermia (TH) in children with return of spontaneous circulation after cardiac arrest (CA) and to assess if microcirculatory impairment predicts mortality. This has been reported for post-CA adults, but results might be different for children because etiology, pathophysiology, and mortality rate differ.
Methods: This prospective observational cohort study included consecutive, non-neonatal post-CA children receiving TH upon intensive care admission between June 2008 and June 2012. Also included were gender-matched and age-matched normothermic, control children without cardiorespiratory disease. The buccal microcirculation was non-invasively assessed with Sidestream Dark Field Imaging at the start of TH, halfway during TH, at the start of re-warming, and at normothermia. Macrocirculatory, respiratory, and biochemical parameters were also collected.
Results: Twenty post-CA children were included of whom 9 died. During hypothermia, the microcirculation was impaired in the post-CA patients and did not change over time. At normothermia, the core body temperature and the microcirculation had increased and no longer differed from the controls. Microcirculatory deterioration was associated with mortality in the post-CA patients. In particular, the microcirculation was more severely impaired at TH start in the non-survivors than in the survivors – positive predictive value: 73–83, negative predictive value: 75–100, sensitivity: 63–100%, and specificity: 70–90%.
Conclusions: The microcirculation is impaired in post-CA children during TH and more severe impairment at TH start was associated with mortality. After the stop of TH, the microcirculation improves rapidly irrespective of outcome.

1. Introduction

Cardiac arrest (CA) in children is associated with a high mortality rate.[1,2] In the children with return of spontaneous circulation (ROSC), significant morbidity is often present and a post-cardiac arrest syndrome (PCAS) develops.[1–3] In view of its beneficial effects on outcome in post-CA adults and asphyxiated neonates, mild therapeutic hypothermia (TH) has been clinically introduced in post-CA children.[4–7] A randomized trial in post-CA children is currently ongoing.[8] While the exact mechanism by which TH improves outcome is unknown, multiple beneficial effects have been suggested, which include balancing of vasoactive mediators and normalizing vasopermeability.[9]

TH should reduce the harmful PCAS effects while adequate macrocirculation and microcirculation is ensured. The microcirculation can now be visualized non-invasively at the bedside with several techniques.[10] These have revealed that in post-CA adults the microcirculation was decreased during TH and that microcirculatory impairment existed while macrocirculatory parameters were

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unaltered.[11,12] Moreover, persistent microcirculatory impairment was associated with mortality.[11] This has also been reported for children with distributive shock.[13]

It is not yet known, however, whether these findings also apply to post-CA children. Extrapolating the findings in post-CA adults to children is probably inappropriate because CA etiology, post-CA pathophysiology, and post-CA mortality rate differ.[3,9,14] Non-invasive microcirculatory monitoring might be particularly valuable for children as the possibilities for invasive hemodynamic monitoring are limited.[15] Therefore, this study aimed to assess whether the microcirculation is impaired during and after TH in post-CA children and to evaluate whether microcirculatory impairment predicts mortality. We hypothesized that microcirculatory alterations would exist during TH and that the microcirculation would predict mortality after TH.

2. Methods

2.1. Study design and setting

This prospective observational cohort study included patients admitted to the intensive care unit (ICU) of a level III university children's hospital between June 2008 and June 2012. The local medical ethical review board approved the study. Parental informed consent was obtained prior to the study start.

2.2. Patients

Children eligible for inclusion were those aged between 28 days and 18 years with post-CA ROSC who received TH after admission to the study site. The exclusion criteria were: denied informed consent, start of TH in a center other than the study site, and failure to induce TH within 12 h after admission. Patients in whom only one microcirculatory measurement was done due to logistic reasons were also excluded. Age-matched and gender-matched normothermic children without cardiorespiratory disease who were hospitalized for minor, elective surgery served as controls.

2.3. Data collection

The modified Utstein reporting templates were followed where possible.[16] Data were obtained within 12 h after the start of TH (T0), at 12–24 h after TH start (T1), within 12 h after starting re-warming (T2), and at normothermia (T3). The primary endpoint was ICU survival. Data were obtained once in the controls.

2.3.1. Microcirculatory perfusion

The microcirculation was studied using Sidestream Dark Field Imaging (MicroVision Medical, Amsterdam, the Netherlands).[17] At three sites in the buccal mucosa, the microcirculation was measured according to the guidelines.[18] To avoid pressure artifacts, we adhered to the standard operating procedure as published by Trzeciak et al.[19] Blinded, randomized video sequences were analyzed offline using dedicated software (Automated Vascular Analysis 3.0, Academic Medical Centre, Amsterdam, the Netherlands). Total vessel density (TVD), perfused vessel density (PVD), proportion of perfused vessels (PPV), microvascular flow index (MFI), and heterogeneity index (HI) were calculated for small (S; $\varnothing \leq 10\,\mu m$) and non-small vessels (NS; $\varnothing$ 11–100 μm) according to the guidelines.[13,18,20,21] HI was calculated as the difference between the highest and the lowest quadrant score that is then divided by the mean score of all quadrants for one measurement. For all other scores, the mean of the video sequences per measurement was taken. The inter-observer variability between two raters was determined for all microcirculatory parameters using video sequences obtained for the current ($n = 60$, 19%) and for another study ($n = 60$, 19%). The Spearman's rank correlation coefficient ranged from 0.533 to 0.932 (all p-values < 0.001; mean $\rho = 0.768$), the intra-class correlation coefficient from 0.565 to 0.869 (all p-values < 0.001; mean $\rho = 0.750$).

2.3.2. Demographic and time-dependent parameters

Patient demographics were collected together with core body temperature, disease severity measures – the vasopressor score (VP-score), the Pediatric cerebral performance category scale (PCPC) at ICU discharge, and the Pediatric logistic organ dysfunction score (PELOD) at ICU day one and two-, macrocirculatory parameters, peripheral capillary refill time (pCRT), respiratory parameters, and biochemical parameters. The VP-score, PCPC score, and PELOD score, respectively serving as measures for cardiovascular, cerebral, and overall disease severity, were determined as previously described.[22–24]

2.4. Hospital treatment protocol

TH – rectal core body temperature 32.0–34.0 °C – was induced as soon as possible after admission using extracorporeal blankets (Blanketrol III, Cincinnati Sub Zero, Cincinnati, USA). Complementary intracorporeal cooling was applied if necessary. According to protocol, all children who received advanced Pediatric life support received TH. During TH, patients received continuous sedation (midazolam, 50–1000 mcg kg^{-1} h^{-1}, morphine, 5–30 mcg kg^{-1} h^{-1}, clonidine, 0.20–1.00 mcg kg^{-1} h^{-1}, and/or propofol, 1–8 mg kg^{-1} h^{-1}) and neuromuscular blockade (vecuronium, 40–100 mcg kg^{-1} h^{-1} and/or rocuronium, 300–700 mcg kg^{-1} h^{-1}) if necessary. After 24 h, patients were re-warmed – 0.25 °C h^{-1} – to normothermia – rectal core body temperature 36.5–37.5 °C. To keep MABP within age-appropriate normal range, fluid resuscitation and cardiovascular drug support were started at the discretion of the attending intensivist. Ventilator settings were set to achieve normoxia (paO_2 12.0–13.3 kPa) and normocapnia (pCO_2 4.0–6.4 kPa). Patients with refractory respiratory failure despite maximal conservative treatment received extracorporeal membrane oxygenation (ECMO).

2.5. Statistical analysis

Continuous data are presented as median (IQR); discrete data as numbers (%). The microcirculatory data were analyzed in two steps. First, differences over time were assessed using mixed effects models with time as single parameter. Linearity was assumed for all models except MFI NS. In the case of overall differences, subtests between time points were performed. Second, the relation between outcome and the microcirculation was assessed with non-parametric tests and through joint modeling – which incorporates both time and outcome as covariate thereby taking into account both the longitudinal and survival effects.[25] If relevant, the area under the curve (AUC) of the receiver operating characteristic (ROC) was determined. Cut-off values were identified and sensitivity, specificity, and positive and negative predictive value were calculated. With the cut-off values, the association between microcirculatory impairment and disease severity was explored. For all other data only step one was performed. Cases were compared to controls using non-parametric tests. Statistics were calculated using IBM SPSS or R statistics 2.15.2. A p-value < 0.050 was considered statistically significant.

Table 1
The baseline patient characteristics. Data are shown for the entire cohort and for the survivors and non-survivors separately.

	Total $N=20$	Survivors $N=11$	Non-survivors $N=9$	p-Value
Male gender, n (%)	15 (75)	10 (91)	5 (56)	0.127
Out-of-hospital CA, *n* (%)	17 (85)	10 (91)	7 (78)	0.566
Witnessed CA, *n* (%)	19 (95)	10 (91)	9 (100)	1.000
Bystander CPR, *n* (%)	12 (60)	6 (67)	6 (75)	1.000
Time first CPR – ROSC in min, median (IQR)	15 (30)	15 (25)	20 (39)	0.818
First monitored rhythm shockable[A], *n* (%)	4 (20)	4 (40)	0 (0)	0.087
First admission to another hospital, *n* (%)	2 (10)	0 (0)	2 (22)	0.189
Age at ICU admission in y, median (IQR)	2.3 (10.6)	1.9 (11.6)	2.8 (8.9)	0790
Weight at ICU admission in kg, median (IQR)	13.0 (31.3)	13.0 (38.3)	13.0 (24.0)	0.675
Time ICU admission – start TH in h, median (IQR)	0 (6)	4 (7)	0 (0)	0.009
Hypothermic at ICU admission, *n* (%)	11 (55)	4 (36)	7 (78)	0.092
First recorded core body temperature in °C, median (IQR)	33.7 (2.3)	35.0 (2.8)	33.4 (2.1)	0.057
PELOD day 1, median (IQR)	33 (10)	32 (10)	33 (14)	0.298
PELOD day 2, median (IQR)	32 (11)	31 (19)	32 (11)	0.331
Absent LPLR at start TH, *n* (%)	4 (20)	0 (0)	4 (50)	0.023
Fluid balance day 1 in ml kg^{-1} d^{-1}, median (IQR)	2.4 (3.5)	2.7 (3.9)	2.1 (3.0)	0.849
Fluid balance day 2 in ml kg^{-1} d^{-1}, median (IQR)	1.5 (2.2)	0.5 (2.2)	2.3 (1.9)	0.138
ECMO, *n* (%)	3 (15)	2 (18)	1 (11)	1.000
PCPC at ICU discharge ≤ 2, *n* (%)	6 (30)	6 (55)	0 (0)	NA
Length of ICU stay in days, median (IQR)	7.6 (7.1)	10.3 (25.7)	4.8 (7.9)	0.030
Diagnosis, *n* (%)				
- Cardiac	9 (45)	6 (55)	3 (33)	0.406
- Respiratory	11 (55)	5 (45)	6 (67)	
Cause of death, *n* (%)				
- Cardiac	2 (10)	–	2 (10)	NA
- Respiratory	1 (5)	–	1 (5)	
- Cerebral	6 (30)	–	6 (30)	

Categorical variables are presented as *n* (%), continuous variables as median (IQR). Differences assessed using non-parametric tests. CA: cardiac arrest, CPR: cardiopulmonary resuscitation, ECMO: extracorporeal membrane oxygenation, h: hours, IQR: interquartile range, LPLR: left pupillary light reflex, min: minutes, ml kg^{-1} d^{-1}: milliliter per kilogram per day, NA: not assessed, PCPC: pediatric cerebral performance category scale, PELOD: pediatric logistic organ dysfunction score, ROSC: return of spontaneous circulation, TH: therapeutic hypothermia, y: years, °C: degrees Celsius.

[A] All shockable rhythms were due to ventricular fibrillation.

3. Results

During the study period 55 patients with ROSC after CA were admitted to our ICU who received TH. Of those 55 eligible patients, 23 (42%) were excluded because of denied consent and 12 (22%) because of logistic reasons. Twenty children were included who received TH at the study site. These patients did not differ from the excluded patients with regards to gender, out-of-hospital CA, survival rate, and percentage of patients with primary cardiac disease.

Table 1 shows the baseline characteristics of the included patients. In 9 (45%) patients, CA was caused by primary cardiac disease – i.e., cardiomyopathy ($n=4$), cardiac arrhythmias ($n=3$), congenital cardiac anomaly ($n=1$), and ALTE ($n=1$). In the other 11 patients, CA was caused by primary respiratory failure – i.e., submersion ($n=5$), infectious respiratory disease ($n=2$), neuromuscular disorder ($n=1$), aspiration ($n=1$), tracheomalacia ($n=1$), and hanging ($n=1$).

Nine (45%) post-CA children died in the ICU. The causes of death were hypoxic–ischemic brain injury ($n=6$), refractory cardiac failure ($n=2$), and refractory respiratory failure ($n=1$). In two out of the six patients with brain injury, the direct cause of death was uncontrollable intracranial pressure increments. In the four others, continuation of therapy was futile as they fulfilled the criteria of brain death. Two (22%) non-survivors did not reach normothermia. Three patients, one non-survivor, received ECMO. In 6 (55%) out of the 11 survivors the PCPC was ≤ 2, indicating that at ICU discharge they had, at worst, mild neurologic deficits and that they were conscious, alert, and deemed capable of age-appropriate interactions. The median first measured body temperature of the non-survivors tended to be lower than that of the survivors. The median time between admission and start of TH was shorter for the non-survivors. More non-survivors than survivors had an absent pupillary reflex at the start of TH.

The 20 control patients without cardiorespiratory failure were all admitted to a surgical ward for minor, elective surgery–i.e., abdominal ($n=7$), urogenital ($n=5$), craniofacial ($n=4$), orthopedic ($n=3$), and thoracic ($n=1$).

3.1. Macrocirculatory, respiratory, and biochemical parameters over time

Table 2 depicts the macrocirculatory, respiratory, and biochemical parameters during and after TH. Apart from core body temperature, the median values for macrocirculatory and respiratory parameters were all within the normal range. Biochemical abnormalities for pH, BE, and arterial lactate were manifested predominantly at the start of TH, while Hb, Ht, and CRP were abnormal predominantly at normothermia.

During TH the core body temperature was below 34.0 °C and it remained unaltered. At normothermia the median (IQR) core body temperature was significantly higher than before: 37.0 (0.3) °C. MABP, arterial saturation, MAP, pCO_2, and the VP-score did not change over time. BE and pH improved halfway TH and remained improved at normothermia. As of the start of re-warming, pO_2 and arterial lactate improved as well. CRP increased while Ht decreased. Hb was lower at normothermia and HR increased.

3.2. The microcirculation over time

The microcirculatory parameters are shown in Fig. 1 and Table 3. Mixed effects models indicated that all microcirculatory parameters except TVD NS changed over time. Subtests for the parameters with an overall difference showed that none improved during TH. At the start of re-warming, all parameters except TVD S and HI S were improved. At normothermia, all microcirculatory parameters except PVD NS and PPV S were improved.

Table 2
The macrocirculatory, respiratory, and biochemical parameters in the post-cardiac arrest children and the normothermic, healthy controls.

	T0 *N* = 18	T1 *N* = 18	T2 *N* = 19	T3 *N* = 18	c0 *N* = 20
Time to start TH in hours[A]	3.6 (4.2)	15.6 (4.4)	28.9 (6.4)	43.4 (8.7)	–
Core body temperature in °C	33.4 (1.6)[b]	33.8 (1.6)[b]	33.9 (1.1)[b]	37.0 (0.3)[a]	36.9 (0.3)
Vasopressor score	0 (13)[b]	8 (22)[b]	10 (20)[b]	9 (26)[b]	0 (0)
Heart rate in bpm	125 (45)	110 (56)	123 (63)	131 (51)[a]	130 (50)
MABP in mm Hg	60 (30)	64 (19)	68 (28)	66 (23)	67 (18)
pCRT in $N < 3$ s/$N \geq 3$ s	1/16	2/15	3/15	6/15	–
MAP in cm H_2O	14 (7)	15 (10)	14 (5)	14 (6)	–
Arterial saturation in %	98 (2)	99 (2)	97 (2)	97 (3)	–
pH	7.27 (0.32)	7.34 (0.12)[a]	7.34 (0.09)[a]	7.38 (0.11)[a]	–
pO_2 in kPa	14.8 (6.4)	13.8 (8.9)	11.4 (5.0)[a]	11.5 (5.5)[a]	–
pCO_2 in kPa	5.1 (2.1)	5.0 (1.2)	5.5 (0.9)	5.1 (1.6)	–
Base excess in mmol L^{-1}	−10 (8)	−5 (4)[a]	−4 (4)[a]	−2 (3)[a]	–
Arterial lactate in mmol L^{-1}	2.8 (5.8)	3.4 (4.5)	2.4 (2.4)[a]	1.5 (0.9)[a]	–
C-reactive protein in mg L^{-1}	1 (5)	23 (51)	80 (78)[a]	73 (85)[a]	–
Hemoglobin in mmol L^{-1}	7.1 (1.0)	7.1 (2.5)	6.6 (1.5)	6.3 (1.5)[a]	–
Hematocrit in L L^{-1}	0.34 (0.07)	0.35 (0.08)	0.31 (0.05)[a]	0.30 (0.05)[a]	–

All data are presented as median (IQR), except pCRT which is in *n* (%).
[a] Indicates change over time from T0 to T3 using mixed effects models and sub-tests.
[b] Indicates difference with c0 using non-parametric tests.
T0: at TH start, T1: halfway during TH, T2: at re-warming start T3: at normothermia in post-cardiac arrest children, c0: normothermic, healthy controls. Bpm: beats per minute, cmH_2O: centimeter water, kPa: kilopascal, L L^{-1}: liter per liter, MABP: mean arterial blood pressure, MAP: mean airway pressure, mg L^{-1}: milligram per liter, mmHg: millimeter mercury, mmol L^{-1}: millimoles per liter, pCRT: peripheral capillary refill time, s: seconds, TH: therapeutic hypothermia, °C: degrees Celsius.

In comparison to the normothermic control patients, TVD S, PVD S, PPV NS, PPV S, MFI NS, MFI S, HI NS, and HI S were all lower during TH in the post-CA patients, while HR or MABP did not differ (Tables 2 and 3). At normothermia, the microcirculatory parameters in the post-CA patients did no longer differ from those in the controls. Significant correlations – range ρ: 0.25–0.45 – existed between core body temperature and PVD S, PPV NS, PPV S, MFI NS, MFI S, and HI S (Fig. 2).

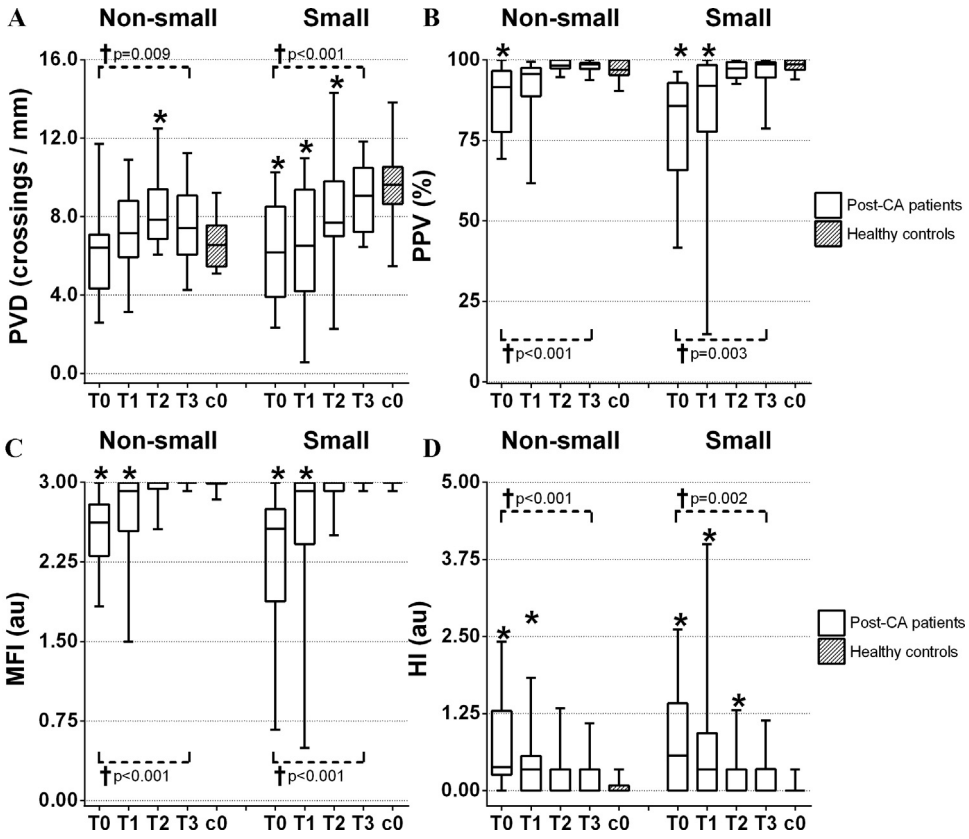

Fig. 1. Boxplots showing the microcirculatory parameters perfused vessel density (A), proportion of perfused vessels (B), microvascular flow index (C), and heterogeneity index (D) for non-small (10 μm ≤ Ø < 100 μm) and small (Ø < 10 μm) vessels in post-cardiac arrest children ($n = 20$; blank boxplots) and normothermic, healthy controls ($n = 20$; obliquely striped boxplots). T0: at TH start, T1: halfway during TH, T2: at re-warming start T3: at normothermia in post-cardiac arrest children, c0: normothermic, healthy controls. † Indicates change over time from T0 to T3 using mixed effects models, * indicates difference with c0 using non-parametric tests.

Table 3
The microcirculatory parameters total vessel density (TVD), perfused vessel density (PVD), proportion of perfused vessels (PPV), microvascular flow index (MFI), and heterogeneity index (HI) for non-small (10 μm ≤ Ø < 100 μm) and small (Ø < 10 μm) vessels in post-cardiac arrest children and normothermic, healthy controls.

	T0 Whole group		T1 Whole group		T2 Whole group		T3 Whole group		c0 Whole group
	Survivors $N = 10$	Non-survivors $N = 8$	Survivors $N = 10$	Non-survivors $N = 8$	Survivors $N = 10$	Non-survivors $N = 9$	Survivors $N = 11$	Non-survivors $N = 7$	$N = 20$
TVD non-small in n mm^{-1}	7.0 (3.2)		8.0 (3.1)		8.0 (2.7)[b]		7.5 (3.0)		6.8 (1.9)
	7.2 (1.8)	5.3 (3.3)	8.7 (2.7)	6.4 (3.5)	7.7 (2.8)	8.5 (3.1)	6.7 (3.6)	7.9 (1.9)	–
PVD non-small in n mm^{-1}	6.4 (2.8)		7.2 (2.9)		7.8 (2.5)[a,b]		7.4 (3.0)		6.5 (2.1)
	6.8 (2.6)[c]	4.3 (2.6)[c]	8.4 (2.4)	6.3 (3.8)	7.5 (2.7)	8.5 (2.9)	6.6 (3.8)	7.8 (2.1)	–
PPV non-small in %	92 (19)[b]		96 (9)		98 (3)[a]		99 (2)[a]		97 (6)
	94 (11)[c]	83 (19)[c]	97 (5)	92 (20)	98 (3)	99 (3)	99 (2)	99 (1)	–
MFI non-small in au	2.62 (0.49)[b]		2.92 (0.46)[b]		3.00 (0.06)[a]		3.00 (0.00)[a]		3.00 (0.05)
	2.74 (0.41)[c]	2.38 (0.64)[c]	2.96 (0.34)	2.72 (0.96)	3.00 (0.00)[c]	2.94 (0.17)[c]	3.00 (0.00)	3.00 (0.00)	–
HI non-small in au	0.38 (1.04)[b]		0.34 (0.56)[b]		0.00 (0.34)[a]		0.00 (0.35)[a]		0.00 (0.34)
	0.36 (0.91)	0.99 (1.24)	0.17 (0.37)	0.37 (0.86)	0.00 (0.35)	0.00 (0.35)	0.00 (0.00)	0.00 (0.38)	–
TVD small in n mm^{-1}	7.4 (3.8)[b]		7.2 (4.7)[b]		8.1 (3.0)		9.2 (3.9)[a]		9.7 (2.8)
	7.7 (4.4)	7.4 (3.1)	9.0 (5.8)	6.7 (2.4)	7.8 (2.9)	8.3 (3.7)	9.1 (2.3)	9.3 (4.5)	–
PVD small in n mm^{-1}	6.2 (4.6)[b]		6.5 (5.2)[b]		7.7 (2.8)[a,b]		9.0 (3.3)[a]		9.6 (2.9)
	7.1 (5.2)	5.6 (2.7)	8.9 (5.8)	5.7 (3.7)	7.5 (2.6)	8.2 (3.7)	9.1 (2.3)	8.9 (4.8)	–
PPV small in %	86 (27)[b]		92 (21)[b]		97 (5)[a]		99 (5)		99 (3)
	91 (14)	70 (28)	94 (11)	90 (29)	98 (4)	95 (5)	99 (5)	98 (5)	–
MFI small in au	2.56 (0.88)[b]		2.92 (0.58)[b]		3.00 (0.08)[a]		3.00 (0.00)[a]		3.00 (0.00)
	2.72 (0.30)[c]	2.08 (1.13)[c]	2.96 (0.21)	2.79 (1.08)	3.00 (0.08)	3.00 (0.17)	3.00 (0.00)	3.00 (0.00)	–
HI small in au	0.57 (1.42)[b]		0.34 (0.93)[b]		0.00 (0.35)[b]		0.00 (0.35)[a]		0.00 (0.00)
	0.37 (1.21)	1.24 (1.29)	0.17 (0.46)	0.36 (1.60)	0.00 (0.53)	0.00 (0.35)	0.00 (0.34)	0.00 (0.38)	–

Data are presented in median (IQR) for the whole cohort (top line) as well as the post-cardiac survivors and non-survivors (bottom line).

[a] Indicates change over time from T0-T3 using mixed effects models and sub-tests.

[b] Indicates difference with c0 using non-parametric tests.

[c] Indicates difference between survivors and non-survivors using non-parametric tests.

T0: at TH start, T1: halfway during TH, T2: at re-warming start T3: at normothermia in post-cardiac arrest children, c0: normothermic, healthy controls.

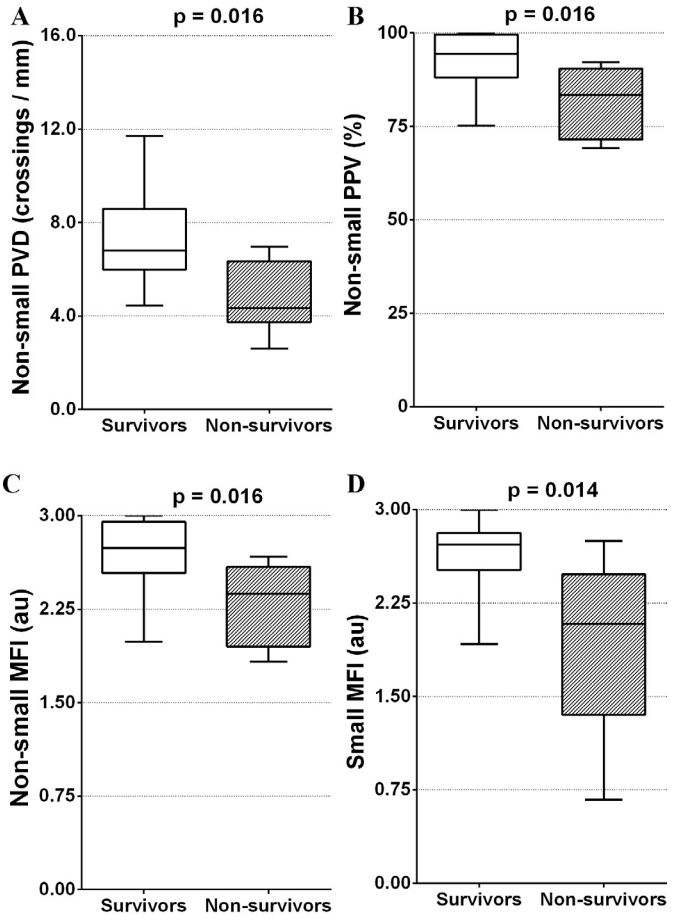

Fig. 2. Boxplots showing the microcirculatory parameters non-small perfused vessel density (A), non-small proportion of perfused vessels (B), non-small microvascular flow index (C), and small microvascular flow index (D) at the start of hypothermia in survivors ($n = 11$; blank box plots) and non-survivors ($n = 9$; obliquely striped box plots). Differences assessed using non-parametric tests.

3.3. Microcirculatory impairment and outcome

At the start of hypothermia, PVD NS, PPV NS, MFI NS, and MFI S were lower in the non-survivors than in the survivors (Fig. 1, Table 3). The AUC of the ROC curves was for all four parameters 0.84 and the best cut-off points for TVD NS, PVD NS, MFI NS, and MFI S at TH start were estimated at 4.9 crossing mm^{-1}, 92%, 2.68 au, and 2.56 au, respectively (Table 4, Supplemental Fig. 1). With these cut-off values, sensitivity ranged from 63 to 100% and specificity ranged from 70 to 90%. The positive and negative predictive value for mortality at ICU discharge ranged from 73 to 83% and from 75 to 100%, respectively. Joint modeling indicated that for every unit increase in PVD NS and MFI S over time – i.e. not only at the start of hypothermia, but also thereafter-, the mortality risk decreased by 5.3 and by 1.1, respectively. For the other microcirculatory parameters, there was no association with mortality over time.

At TH start, the cut-off values according to vessel size – TVD NS, PVD NS, and MFI NS vs. MFI S – then served to stratify the disease severity measures arterial lactate over time, VP-score over time, PELOD at day one and two of ICU admission, and PCPC at ICU discharge (supplemental digital content Table 1). In this way it became apparent that patients with microcirculatory deterioration in the non-small vessels – i.e., TVD NS, PVD NS, and MFI NS – had higher arterial lactate levels at normothermia; had higher VP-scores halfway during TH, at the start of re-warming, and at normothermia; and had higher a PCPC score at ICU discharge. Likewise, patients with lower MFI S had microcirculatory deterioration had a higher PCPC score at ICU discharge.

At the start of TH, neither the core body temperature nor the macrocirculatory, respiratory, or biochemical parameters differed between the survivors and the non-survivors, apart from BE which was unfavorable for the non-survivors (supplemental digital content Table 2).

4. Discussion

This study demonstrates that the buccal microcirculation was impaired during TH in post-CA children, while the cardiorespiratory parameters were relatively unaffected. After TH, the microcirculation improved to a level comparable to normothermic children without cardiorespiratory disease. Microcirculatory impairment was associated with mortality in the post-CA patients. In particular, at the start of TH, the microcirculation was more severely deteriorated in the non-survivors than in the survivors.

This study is the first to describe that the buccal microcirculation is altered during TH in post-CA children. Similar findings have been reported for post-CA adults and perinatally asphyxiated neonates.[11,12,26] The current study is unique in studying the microcirculation shortly after re-warming. At this point, the microcirculation had already improved substantially while neither core body temperature, nor the macrocirculatory or respiratory parameters had changed. This confirms that in post-CA children microcirculatory function cannot be estimated by macrocirculatory parameters, as was also reported for post-CA adults.[11] Interestingly, microcirculatory improvement coincided with improvements in arterial lactate and pO_2, while pCRT remained abnormal over time.

Microcirculatory impairment before and after TH predicted mortality in post-CA adults, whereas we found the microcirculation to be lower in non-survivors at TH start.[11] Differences in etiology can explain this discrepancy: all of the adults had primary cardiac disease as opposed to 50% of the children.[11] There are also pathophysiologic differences: PCAS develops differently in children and continuous post-CA macrocirculatory failure is less prominent.[3] Accordingly, cerebral injury rather than cardiac disease is the predominant determinant for outcome in children.[3,27–29] Our data supported this as 75% of the non-survivors were brain death and both HR and MABP were within the normal range throughout follow-up.

In critically ill adults, therapy efficacy and outcome could be predicted by early microcirculatory monitoring.[30,31] We show that, next to mortality, microcirculatory impairment at TH start is associated with cardiovascular disease severity and neurologic disease severity later in time So, non-invasive microcirculatory monitoring might be clinically valuable in post-CA children. For children – and infants in particular – the possibilities for (invasive) cardiovascular monitoring are limited.[15]

In the present study, microcirculatory impairment was associated with poor outcome at TH start in particular. At this point, pupillary reflexes were absent more often and BE, pH, and arterial lactate either differed or tended to differ suggesting that the non-survivors were in a worse clinical condition. Additionally, PCAS is still in its early phase at TH start and includes amongst others inflammation and continuous ischemia.[3,9,32] Hypothetically, both could have contributed to the microcirculatory impairment in our patients.[3,9,32] We, however, did not measure SvO_2, interleukins, or complement factors. Furthermore, TH is acknowledged to improve outcome in post-CA adults and perinatally asphyxiated neonates.[4–7] Yet, non-clinical studies indicate that TH in itself decreases the microcirculation.[33] During TH, microcirculatory deterioration could either be an epiphenomenon or an active mediator through which TH partly exerts its beneficial effects. The

Table 4
The value for predicting mortality in post-cardiac arrest children with the microcirculatory parameters non-small perfused vessel density (TVD), non-small proportion of perfused vessels (PPV), non-small and small microvascular flow index (MFI).

	AUC (95%-CI)	Cut-off value	Sensitivity in % (95%-CI)	Specificity in % (95%-CI)	Positive predictive value (95%-CI)	Negative predictive value (95%-CI)
PVD non-small in n mm^{-1}	0.84 (0.65–1.00)	4.9	63 (24–91)	90 (55–100)	83 (36–100)	75 (43–95)
PPV non-small in n mm^{-1}	0.84 (0.65–1.00)	92	100 (63–100)	70 (35–100)	73 (34–94)	100 (59–100)
MFI non-small in au	0.84 (0.64–1.00)	2.68	100 (63–100)	70 (35–100)	73 (34–94)	100 (59–100)
MFI small in au	0.84 (0.65–1.00)	2.56	88 (47–100)	80 (44–97)	78 (40–97)	89 (52–100)

AUC: area under the receiver operating characteristic, 95%-CI: 95% confidence interval, n mm^{-1}: number per millimeter, au: arbitrary units.

latter would contrast our observation that microcirculatory impairment relates to poor outcome. Thus, our results suggest that TH improves outcome by impacting enzymatic and metabolic processes predominantly.[3,9,32]

Although core body temperature did not differ at the time of the microcirculatory measurements, we did observe that hypothermia was more rapidly induced in the non-survivors and that the first recorded temperature tended to be lower. This was observed before.[34] Neither the underlying diagnoses, nor the number of near-drownings differed in our study and hospital protocol applied to all patients. In contrast, our neurologic and biochemical measurements suggest that the more rapidly induced hypothermia most likely resulted from the non-survivors' poor clinical condition. Non-induced hypothermia occurs as often as hyperthermia and conveys an increased mortality risk as well.[35,36] Endogenous factors attributing to non-induced hypothermia include altered basal metabolic rate, impaired cortisol release, hypothalamic temperature set-point alterations, vasoconstriction, and absent shivering.[35]

Absent pupillary reflexes and lower pH are independently associated with mortality in post-CA children.[3,36] Future research should focus on the combination of parameters that best predict poor outcome or monitor therapy efficacy. Our study shows that non-invasive microcirculatory monitoring could be considered as covariate in future studies, but also that the predictive accuracy of microcirculatory monitoring in post-CA children should be detailed better and that the functional role of the microcirculation during PCAS and TH should be elucidated.

4.1. Limitations

Several limitations must be acknowledged. Above all, few data regarding the period prior to ICU admission were available so it is unclear to what extent the proceedings during the resuscitation period biased our findings. Furthermore, the included cohort was modest in size and quite heterogeneous. For instance, two patients were first admitted to another hospital. Also, CPR time and lactate levels were relatively short/low. Relatively many patients were excluded. Results should thus be interpreted cautionately, given that data were obtained only in the patients who received TH at the study site. Multicenter trials are therefore needed to substantiate our findings. Furthermore, owing to the observational design, our findings are associative rather than causal. Also, microcirculatory monitoring was limited to the very early post-CA phase whereas the follow-up for survival was longer. In addition, a reliable pre-hypothermic microcirculatory assessment was not possible.

5. Conclusions

In non-neonatal post-CA children, the microcirculation is impaired during TH and improves rapidly after TH discontinuation. Microcirculatory impairment early after the start of TH is associated with poor outcome. Future studies should evaluate in greater detail the accuracy by which microcirculatory monitoring predicts outcome and whether it can be used to assess therapy efficacy.

Conflict of interest statement

The other authors state that they hold no financial interest in the products/drugs mentioned within this article and report no conflicts of interest with the exception of CI. CI is the inventor of the Sidestream Dark Field Imaging technology and holds shares in MicroVision Medical. He has served as a consultant for this company in the past, but has ended all contact for more than four years. CI has no other competing interests in this field beyond his commitment to promoting the importance of the microcirculation with regard to patient. The other authors state that they hold no financial interest in the products/drugs mentioned within this article and report no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2013.10.024.

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